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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/491,500	01/26/00	BLACK	K	CEDAR043-453

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EXAMINER	
NIKODEM,D	
ART UNIT	**PAPER NUMBER**
1633	3

DATE MAILED: 06/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary	Application No. 09/491,500	Applicant(s) BLACK ET AL.	
	Examiner David Nikodem	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-109* is/are pending in the application.

4a) Of the above claim(s) *35-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34 and 97-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-34 and 97-109, drawn to method of delivery of an agonist to an abnormal brain region to increase permeability and/or potassium flux, classified as unclassifiable since the agonist does not appeared to be identified.

II. Claims 35-109, drawn to method of delivery of an agonist to a malignant tumor to increase permeability and/or potassium flux, and method of treatment thereof, classified as unclassifiable since the agonist does not appeared to be identified.

Note that claims 97-109, drawn to pharmaceutical compositions and kits, are generic to each Groups I and II. Upon election, claims 97-109 will be examined only to the extent that they read on the elected invention. Additionally, applicants are required to amend claims 97-109 to read on the elected invention, since the claims are generic to Groups I and II, and upon election will contain non-elected subject matter.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In

the instant case the different inventions are not disclosed as capable of use together since the inventions are directed to the treatment of two different diseases/afflictions. The methods to use each invention have different scientific considerations such as the delivery of an agonist to different tissues. Further, the two inventions require different modes of operation, including different methods of delivery, and different adminsterable formulations of the agonist. Each invention is capable of supporting an individual patent and thus, the inventions are patentable distinct and the required search would not be coextensive.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as demonstrated by their different classification and recognized divergent subject matter and because inventions I-IV require different searches that are not coextensive, examination of these claims would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Nisan Stienberg on May 31, 2000 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-34. Affirmation of this election must be made by applicant in replying to this Office action. Claims 35-96 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 97-109 are generic and will be examined with the elected Group.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one

or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102((e), f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-34 and 97-109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Black (U.S. Patent No. 5,434,137), in view of the combination of Sobey, *et al.* and Cherksey.

9. The claims are drawn to a method of delivering a medicant to an abnormal brain region in a mammal comprising administering a potassium channel agonist, other than

bradykinin or a bradykinin analog, under conditions that increase potassium flux, and/or increase permeability of arterioles or capillaries that deliver blood to the abnormal brain region, and the simultaneous delivery of said medicant so that said medicant is selectively delivered to cells of said abnormal brain region. The claims are further drawn to limitations of the broad breadth of the above method, including, type of abnormal brain region (stroke-affected, ischemia-affected, tumor, *etc.*), type of medicants (diagnostic agents, cytokine, nucleotide analog, *etc.*), type of delivery (intracarotid injection, intraarterial injection, *etc.*), dosages (0.075-1500 μg/Kg, *etc.*), type of mammal (human, canine, feline, *etc.*), and rates of delivery (μg/Kg,min, *etc.*). The claims are further drawn to pharmaceutical compositions and kits comprising a potassium channel agonist, other than bradykinin or a bradykinin analog, formulated for intravascular infusion or injection with said medicant. The aforementioned limitations upon the medicant, the agonist, type of abnormal brain region, type of mammal, type of dosage, and rates of delivery apply for the pharmaceutical compositions. Further limitations upon the pharmaceutical compositions include an acceptable buffer solution, including phosphate buffered saline. Limitations upon the kit include instructions and the aforementioned types of agonist.

10. Black (U.S. Patent No. 5,434,137) teaches (specification and claims 1-6) a method for selectively opening abnormal brain tissue capillaries of a mammal in order to allow selective passage of neuropharmaceutical agents into abnormal brain tissue. The method uses infusion of bradykinin into the carotid artery. The reference further teaches that bradykinin selectively opens abnormal brain tissue capillaries without

opening normal brain capillaries and that the invention can be used for brain tumors and abnormal tissue resulting from ischemia, multiple sclerosis, cerebral abscess, and any number of different diseases. The reference further teaches that any number of the multitude of well-known neuropharmaceutical agents and/or diagnostic agents can be used. The reference further teaches intra-arterial and intracarotid injection, preferred dosages and preferred rates of delivery. The reference further teaches a pharmaceutical formulation of the aforementioned method, in any of the well-known pharmaceutical carriers, including 0.9% saline. The reference fails to teach that bradykinin is a potassium channel agonist or that it increases potassium flux.

11. Sobey, *et al.* teaches vasodilator responses of cerebral arterioles to bradykinin involve the activation of potassium channels, thus increasing potassium flux and potassium concentrations.

12. Additionally, activators/agonists of potassium channels were well known in the art at the time of filing. For example, Cherksey teaches (page 4) a multitude of potassium channel agonists, including: RP52891, cromakalim, lemakalim, celikalim, RO316930, 507-PC0-400, HOE-234, minoxidil, diazoxide, pinacidil and nicorandil.

13. Therefore, in view of such, it would have been obvious for one of ordinary skill in the art to determine that the action of allowing selective passage of neuropharmaceutical agents into abnormal brain tissue, as taught by Black, is based on the activation of potassium channels, as taught by Sobey, *et al.*. It would have been further obvious for one skilled in the art to utilize other potassium channel activators, or agonist, as taught by Cherksey, to achieve the same effect taught by Black. One would

have been motivated to do so in order to provide for the benefit of selectively treating abnormal brain regions, as taught by Black, using potassium channel agonists other than bradykinin that may provide for better membrane permeability and/or potassium channel activation in certain abnormal brain region states and thus better drug delivery efficacy.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

15. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

16. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 1-5, 7-9, 11, 12, 14-22, 24-26 and 28-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,434,137 in view of Sobey, *et al.* and Cherksey.

18. The claims of the instant application have been described in paragraph 9 of the instant office action. The claims of the patent are drawn to a method for selectively delivering a neuropharmaceutical or diagnostic agent to abnormal brain tissue present in a mammal, comprising the infusion of bradykinin or a bradykinin analog and the administration of a therapeutic amount of a neuropharmaceutical agent and/or diagnostic agents consisting of cisplatin, carboplatin, methotrexate, 5-FU, amphotericin, monoclonal antibodies, 99-Tc glucoheptonate, gallium-EDTA, ferrous magnetic contrast agents and iodinated contrast agents. The claims are further drawn to limitations of dosages of bradykinin or bradykinin analogs.

19. The teachings of Sobey, *et al.* and Cherksey have been described in paragraphs 11 and 12, respectively, of the instant office action.

20. Therefore, in view of such, it would have been obvious for one of ordinary skill in the art to determine that the action of allowing selective passage of neuropharmaceutical agents into abnormal brain tissue, as taught by Black, is based on the activation of potassium channels, as taught by Sobey, *et al.*. It would have been further obvious for one skilled in the art to utilize other potassium channel activators, or agonist, as taught by Cherksey, to achieve the same effect taught by Black. One would have been motivated to do so in order to provide for the benefit of selectively treating abnormal brain regions, as taught by Black, using potassium channel agonists other

than bradykinin that may provide for better membrane permeability and/or potassium channel activation in certain abnormal brain region states and thus better drug delivery efficacy.

21. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Nikodem whose telephone number is (703) 308-8361. The examiner can normally be reached on M-F, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3230 for regular communications and (703) 305-3230 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1123.

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June 19, 2000

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
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